Bioorganic Chemistry 83 (2019) 161–169

Contents lists available at ScienceDirect

Bioorganic Chemistry

journal homepage: www.elsevier.com/locate/bioorg

Design and synthesis of novel quinazolinone-1,2,3-triazole hybrids as new anti-diabetic agents: *In vitro* α-glucosidase inhibition, kinetic, and docking study

Mina Saeedi[a,b], Maryam Mohammadi-Khanaposhtani[c], Parvaneh Pourrabia[b], Nima Razzaghi[d], Reza Ghadimi[e], Somaye Imanparast[f], Mohammad Ali Faramarzi[f], Fatemeh Bandarian[g], Ensieh Nasli Esfahani[g], Maliheh Safavi[h], Hossein Rastegar[i], Bagher Larijani[j], Mohammad Mahdavi[j,*], Tahmineh Akbarzadeh[d,b,*]

[a] Medicinal Plants Research Center, Faculty of Pharmacy, Tehran University of Medical Sciences, Tehran, Iran
[b] Persian Medicine and Pharmacy Research Center, Tehran University of Medical Sciences, Tehran, Iran
[c] Cellular and Molecular Biology Research Center, Health Research Institute, Babol University of Medical Sciences, Babol, Iran
[d] Department of Medicinal Chemistry, Faculty of Pharmacy, Tehran University of Medical Sciences, Tehran, Iran
[e] Social Determinants of Health Research Center, Health Research Institute, Babol University of Medical Sciences, Babol, Iran
[f] Department of Pharmaceutical Biotechnology, Faculty of Pharmacy and Biotechnology Research Center, Tehran University of Medical Sciences, Tehran, Iran
[g] Diabetes Research Center, Endocrinology and Metabolism Clinical Sciences Institute, Tehran University of Medical Sciences, Tehran, Iran
[h] Department of Biotechnology, Iranian Research Organization for Science and Technology, P.O. Box 3353-5111, Tehran, Iran
[i] Food and Drug Research Institute, Food and Drug Administration, MOHE, Tehran, Iran
[j] Endocrinology and Metabolism Research Center, Endocrinology and Metabolism Clinical Sciences Institute, Tehran University of Medical Sciences, Tehran, Iran

ARTICLE INFO

This paper is dedicated to the memory of Professor Abbas Shafiee (1937–2016)

Keywords:
Anti-diabetic activity
Competitive inhibition
α-Glucosidase
Molecular docking
Quinazolinone
1,2,3-Triazole

ABSTRACT

A novel series of quinazolinone-1,2,3-triazole hybrids **10a-p** were designed, synthesized, and evaluated for their *in vitro* α-glucosidase inhibitory activity leading to efficient anti-diabetic agents. All synthesized compounds exhibited good inhibitory activity against yeast α-glucosidase (IC_{50} values in the range of 181.0–474.5 μM) even much more potent than standard drug acarbose (IC_{50} = 750.0). Among them, quinazolinone-1,2,3-triazoles possessing 4-bromobenzyl moiety connected to 1,2,3-triazole ring (**10g** and **10p**) demonstrated the most potent inhibitory activity towards α-glucosidase. Compound **10g** inhibited α-glucosidase in a competitive manner with K_i value of 117 μM. Furthermore, the binding modes of the most potent compounds **10g** and **10p** in the α-glucosidase active site was studied through *in silico* docking studies. Also, lack of cytotoxicity of compounds **10g** and **10p** was confirmed *via* MTT assay.

1. Introduction

α-Glucosidase is a key enzyme in the process of digestion of carbohydrates. It breaks down starch and disaccharides to glucose leading to the release of absorbable monosaccharides and consequently increase of blood glucose levels. In this respect, it has been considered as a therapeutic target for the treatment of type 2 diabetes [1,2] since enzyme inhibition delays carbohydrate digestion and monosaccharide absorption and subsequently reduces postprandial plasma glucose levels and postprandial hyperglycemia [3]. Currently prescribed α-glucosidase inhibitors such as acarbose, voglibose, and miglitol have depicted different side effects including bloating, diarrhea, flatulence, pain, and abdominal discomfort [4]. Hence, discovery and development of new α-glucosidase inhibitors possessing high efficacy and low side effects are still in high demand as an attractive target for medicinal chemists.

Quinazoline and its derivatives have been found as effective and versatile pharmacophoric units in medicinal chemistry to design and develop a wide range of bioactive compounds. Some medicinal properties such as anticancer, antimicrobial, anti-diabetic, anti-cholinesterase, anti-inflammatory, and dihydrofolate reductase inhibitory activities have been successfully documented in the literature [5–11]. Furthermore, recent studies confirmed α-glucosidase inhibitory activity of quinazolines [12–14]. For example, different derivatives of compound **A** (Fig. 1) were found to be potent α-glucosidase inhibitors (IC_{50} = 12.5–15.6 μM comparing with acarbose, 475.0 μM) [14].

* Corresponding authors at: Department of Medicinal Chemistry, Faculty of Pharmacy, Tehran University of Medical Sciences, Tehran, Iran (T. Akbarzadeh).
E-mail addresses: momahdavi@tums.ac.ir (M. Mahdavi), akbarzad@tums.ac.ir (T. Akbarzadeh).

https://doi.org/10.1016/j.bioorg.2018.10.023
Received 12 August 2018; Received in revised form 4 October 2018; Accepted 10 October 2018
Available online 11 October 2018

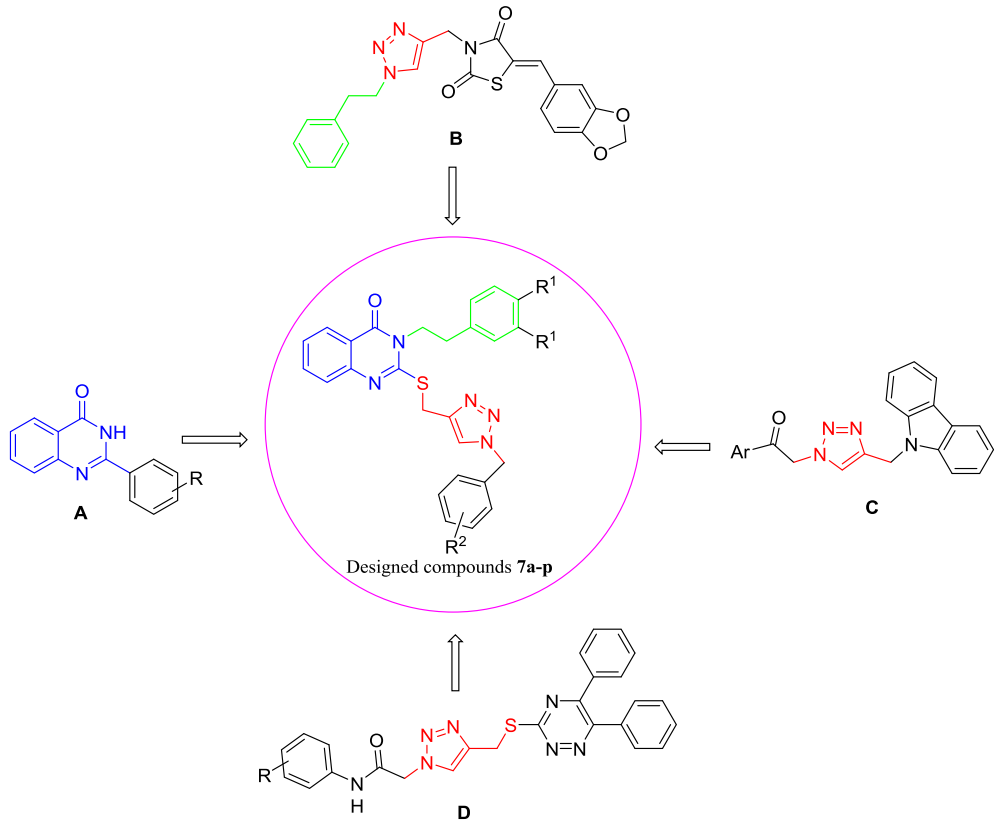


Fig. 1. Design strategy of novel quinazolinone derivatives as novel *α*-glucosidase inhibitors based on molecular hybridization of pharmacophoric units of potent reported *α*-glucosidase inhibitors **A-D**.

1,2,3-Triazole derivatives are undeniably important scaffold in medicinal chemistry. There are various compounds containing 1,2,3-trizole moiety with diverse pharmacological activities such as anticancer, anti-cholinesterase, anti-oxidant, anticonvulsant activities [15–18]. However, several 1,2,3-triazole derivatives with high *α*-glucosidase inhibitory activity have been reported [19–22]. In this respect, Chinthala et al. reported a derivative of 1,2,3-triazole containing phenethyl side chain and thiazolidinedione moiety **B** (Fig. 1) as a potent *α*-glucosidase inhibitor (IC_{50} = 0.3 μM comparing with acarbose, 12.5 μM) [20]. Hybrid structures of 1,2,3-triazole and different heterocycles such as carbazole (**C**) (IC_{50} = 0.8–100.8 μM comparing with acarbose, 840 μM) or triazine rings (**D**) (IC_{50} = 11.6–37.4 μM comparing with acarbose, 817.4 μM) (Fig. 1) were also reported as highly potent *α*-glucosidase inhibitors [21,22].

Molecular hybridization (MH) is a useful tool for design and development of new biologically active compounds which combines two or more pharmacophores to create a new hybrid molecule with improved potency [23]. In continuation of our efforts in design and development of novel *α*-glucosidase inhibitors [24–27] and focusing on compounds **A**, **B**, **C**, and **D** possessing high *α*-glucosidase inhibitory activity, herein, novel quinazolinone-1,2,3-triazole hybrids **10a-p** are reported based on MH. All compounds were synthesized in good yields and evaluated for their *in vitro* *α*-glucosidase inhibitory activity. To investigate the interaction of the title compounds with amino acid residues participating in the *α*-glucosidase, kinetic and molecular docking studies were also performed.

2. Results and discussion

2.1. Chemistry

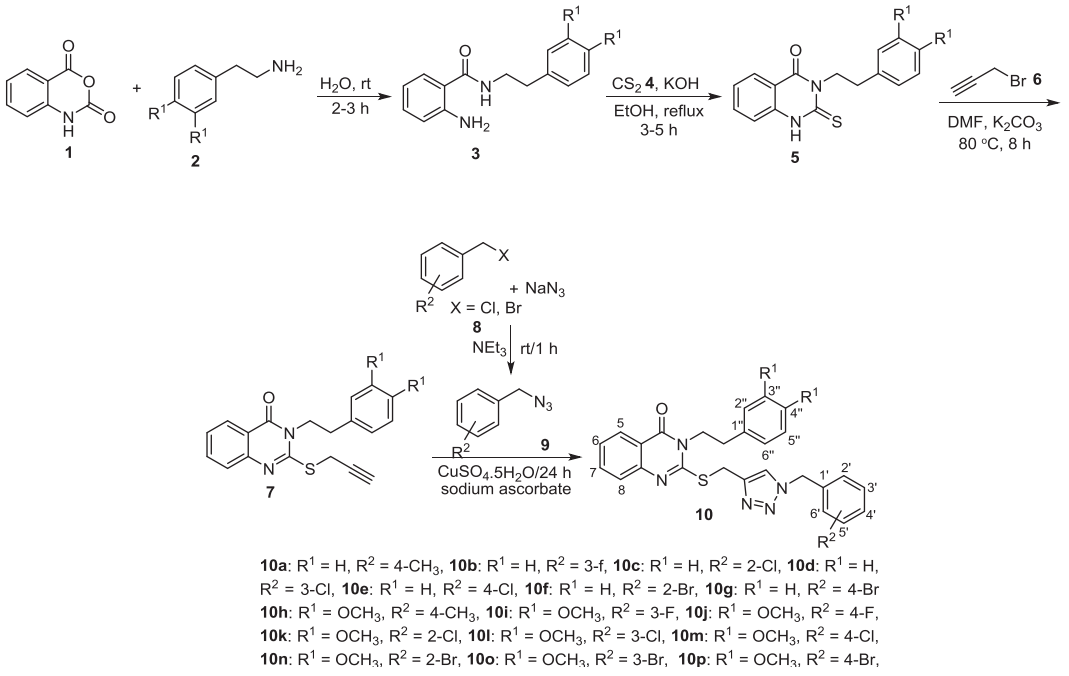
Synthesis of desired compounds **10a-p** was performed as outlined in Scheme 1. Required starting materials, 2-amino-*N*-arylbenzamide derivatives **3** were obtained by the reaction of isatoic anhydride **1** and amine **2** in water at room temperature. Then, reaction of compound **3** and carbon disulfide (CS_2) **4** in the presence of potassium hydroxide (KOH) in EtOH by heating at reflux gave the corresponding thioxo-dihydroquinazolinone derivatives **5**. Next, the reaction of compounds **5** and propargyl bromide **6** in the presence of potassium carbonate (K_2CO_3) in DMF by heating at 80 °C afforded propargylated derivatives **7**. Finally, click reaction of compounds **7** and *in situ* prepared organic azides **9** in the presence of trimethylamine and catalytic amounts of $CuSO_4{\cdot}5H_2O$ in the mixture of water/*tert*-butyl alcohol provided the title compounds **10a-p**.

2.2. In vitro α-glucosidase inhibitory activity

All synthesized compounds **10a-p** were evaluated for their *in vitro* inhibitory activity against *α*-glucosidase (*Saccharomyces cerevisiae*) in comparison to acarbose as the standard drug (Table 1). As can be seen in Table 1, synthesized compounds can be divided into two groups; (*i*) derivatives having 3-phenethyl group (**10a-g**) and (*ii*) derivatives having 3-(3,4-dimethoxyphenethyl) group (**10h-p**) connected to quinazoline moiety.

IC_{50} values of the title compounds (ranging from 181.0 to 474.5 μM) revealed that all of them possessed higher inhibitory activity against yeast *α*-glucosidase than acarbose (IC_{50} = 750.0 μM). Compounds **10g** and **10p** containing 4-bromobenzyl moiety connected to 1,2,3-triazole ring demonstrated the highest activity (181.0 and 192.3 μM, respectively). Also, compounds **10a**, **10n**, **10j**, and **10f** exhibited good *α*-glucosidase inhibitory activity with IC_{50} values of 200.0, 202.5, 205.6, and 209.4 μM, respectively.

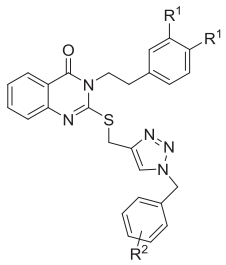
The *α*-glucosidase inhibitory activity of the first group containing 3-phenethyl derivatives **10a-g** demonstrated that compound **10g** containing 4-bromobenzyl moiety was the most potent compound. Changing the position of bromine to the *ortho* position of benzyl group



10a: R^1 = H, R^2 = 4-CH_3, **10b**: R^1 = H, R^2 = 3-f, **10c**: R^1 = H, R^2 = 2-Cl, **10d**: R^1 = H, R^2 = 3-Cl, **10e**: R^1 = H, R^2 = 4-Cl, **10f**: R^1 = H, R^2 = 2-Br, **10g**: R^1 = H, R^2 = 4-Br **10h**: R^1 = OCH_3, R^2 = 4-CH_3, **10i**: R^1 = OCH_3, R^2 = 3-F, **10j**: R^1 = OCH_3, R^2 = 4-F, **10k**: R^1 = OCH_3, R^2 = 2-Cl, **10l**: R^1 = OCH_3, R^2 = 3-Cl, **10m**: R^1 = OCH_3, R^2 = 4-Cl, **10n**: R^1 = OCH_3, R^2 = 2-Br, **10o**: R^1 = OCH_3, R^2 = 3-Br, **10p**: R^1 = OCH_3, R^2 = 4-Br,

Scheme 1. Synthesis of quinazolinone-1,2,3-triazole hybrids **10a-p**.

Table 1
The IC_{50} values of compounds **10a-p** against α-glucosidase.



Compound	R^1	R^2	IC_{50} (μM)[a]
10a	H	4-CH_3	200.0 ± 0.8
10b	H	3-F	426.4 ± 1.5
10c	H	2-Cl	220.5 ± 1.2
10d	H	3-Cl	369.0 ± 1.5
10e	H	4-Cl	474.5 ± 1.0
10f	H	2-Br	209.4 ± 1.5
10g	H	4-Br	181.0 ± 1.4
10h	OCH_3	4-CH_3	301.5 ± 2.2
10i	OCH_3	3-F	250.0 ± 1.2
10j	OCH_3	4-F	205.6 ± 1.0
10k	OCH_3	2-Cl	222.0 ± 1.0
10l	OCH_3	3-Cl	235.8 ± 1.3
10m	OCH_3	4-Cl	463.0 ± 0.6
10n	OCH_3	2-Br	202.5 ± 1.2
10o	OCH_3	3-Br	226.0 ± 0.8
10p	OCH_3	4-Br	192.3 ± 1.8
Acarbose	–	–	750.0 ± 1.5[b]

[a] Data are expressed as mean ± SE (three independent experiments).
[b] IC_{50} values of 856 ± 5.60 and 840 ± 1.73 were also reported for acarbose [28,29].

(compound **10f**) reduced activity (IC_{50} = 209.4 μM). Introduction of other halogens (F and Cl) into the benzyl moiety connected to 1,2,3-triazole ring led to lower activity than compound **10g**. Substitution of fluorine at the *meta* position of benzyl moiety (compound **10b**) gave inhibitory activity with IC_{50} = 426.4 μM. Also, the presence of chlorine at different positions of benzyl group (compounds **10c**, **10d**, and **10e**) afforded various inhibitory activity, however, lower than compound **10g**. Compound **10c** possessing 2-chlorobenzyl group showed IC_{50} = 220.5 μM and changing the position of Cl from *ortho* to *meta* (compound **10d**) and *para* (compound **10e**) led to IC_{50}s = 369.0 and 474.5 μM, respectively. Interestingly, the α-glucosidase inhibitory activity of compounds **10a-g** was not only affected by the electronic property of halogens but also by their position on the benzyl moiety in such a manner that 2-Cl derivative (**10c**) > 4-Cl derivative (**10e**) while 4-Br derivative (**10 g**) > 2-Br derivative (**10f**). Finally, introduction of methyl group into 4-position of pendant benzyl group (compound **10a**) led to good activity (IC_{50} = 200.0 μM). Comparing the inhibitory activity of compounds **10a**, **10e**, and **10g** which have different substituents at 4-position of benzyl moiety showed the order of inhibitory activity as 4-Br > 4-Me > 4-Cl.

Considering the IC_{50} values obtained from the second category containing 3-(3,4-dimethoxyphenethyl) group **10h-p** showed some similarities comparing with their counterparts in the first category (**10a-g**). In this group, 4-Br derivative (compound **10p**) was the most potent compound (IC_{50} = 192.3 μM), however, lower active than its counterpart **10g** (IC_{50} = 181.0 μM). Changing the position of the bromine on the pendant benzyl group from *para* to *meta* (compound **10o**) and *ortho* (compound **10n**) slightly decreased α-glucosidase inhibitory activity with IC_{50}s = 226.0 and 202.5 μM, respectively. They were approximately as potent as their counterparts in the first group. Replacement of Br by F and Cl diminished inhibitory activity and similarly the lowest inhibitory activity was obtained by 4-Cl derivative (compound **10m**, IC_{50} = 463.0 μM). Substitution of Cl at the *ortho* and *meta* positions (compounds **10k** and **10l**) gave IC_{50}s = 222.0 and 235.8 μM, respectively. In the case of 2-Cl derivative (compound **10k**), it was approximately as potent as its counterpart compound **10c**, however, compound **10k** was stronger than compound **10d**. Fluorinated derivatives (compounds **10i** and **10j**) were found to be good α-glucosidase inhibitors with IC_{50}s = 250.0 and 205.6 μM, respectively. Although they were a little lower active than brominated derivatives but much more active than their counterparts in the first category of the synthesized compounds. Finally, insertion of methyl group (compound **10h**) deteriorated α-glucosidase inhibitory activity (IC_{50} = 301.5 μM); also, it showed lower activity than its counterpart **10a**.

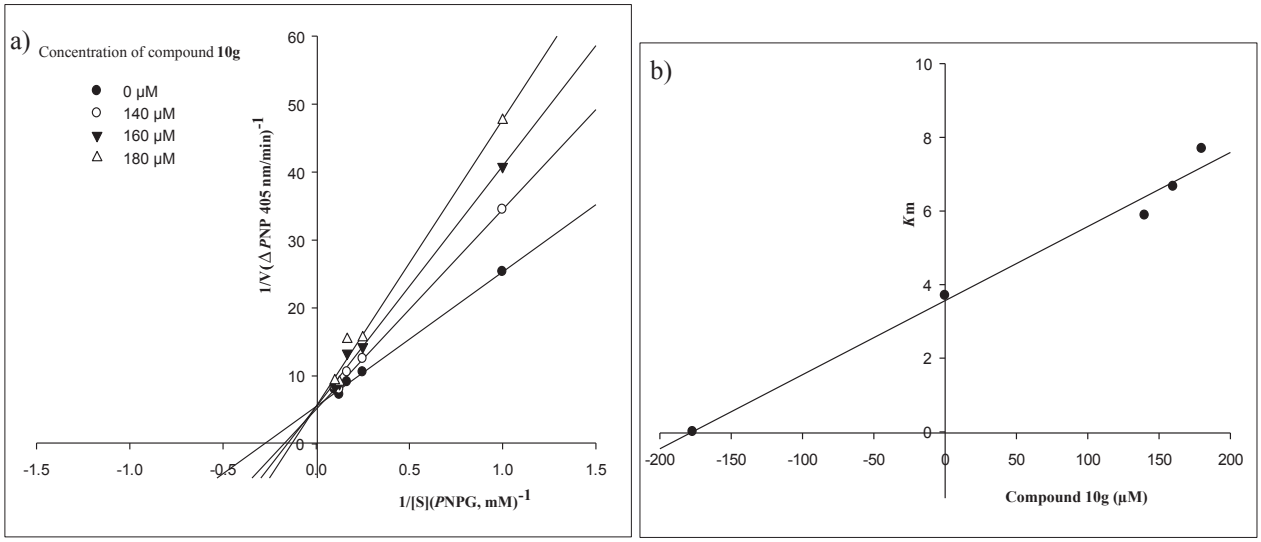


Fig. 2. Kinetic studies of *α*-glucosidase inhibition by **10g**: (a) The Lineweaver–Burk plot in the absence and presence of different concentrations of **10g**, (b) The secondary plot between K_m and various concentrations of **10g**.

2.3. Kinetic study

Kinetic study of the most potent inhibitor of *α*-glucosidase **10g** was performed in order to gain further insight into the mechanism of action of this compound (Fig. 2). The analysis of obtained Lineweaver–Burk plots revealed that no change was observed in V_{max} values by increasing the concentration of inhibitor while K_m values increased. It indicated that compound **10g** was a competitive inhibitor towards *α*-glucosidase (Fig. 2a). The K_i value was calculated as 117 μM through the secondary re-plot of mentioned Lineweaver–Burk plots against the different concentrations of compound **10g**.

2.4. Cytotoxicity studies

As growth and proliferation of cancerous cells are very rapid, cytotoxicity of all synthesized compounds **10a-p** was evaluated against breast cancer cell line MCF-7. Also, the most active compounds **10g** and **10p** were evaluated against normal cell line HDF using MTT assay [24]. Synthesized compounds depicted no cytotoxic activity against each of the two series of cell lines.

2.5. Docking study

Interaction modes of the most potent compounds **10g** and **10p** in the active site of *α*-glucosidase were performed using homology model of *α*-glucosidase according to our previous study [26]. Superposed structure of the standard drug acarbose and the most potent compound **10g** in the active site of homology model of *α*-glucosidase was shown in Fig. 3. The detailed binding mode of acarbose revealed that it interacted with residues Asn241, His279, Glu304, Arg312, Thr302, Thr307, Ser308, and Gln322 (Fig. 4).

The most active compound **10g** established interactions with residues His279, Pro309, Arg312, Val305, and Val316 (Fig. 5a). Quinazolinone moiety formed a hydrogen bond and a π–π interaction with His279. Phenethyl group and sulfur of compound **10g** interacted with Arg312. Also, a hydrophobic interaction between Pro309 and 1,2,3-triazole ring was observed. Moreover, 4-bromobenzyl group showed two interactions with Val305 and Val316 through 4-bromo substituent and a hydrophobic interaction with Pro309 through phenyl ring.

Introduction of two methoxy groups at 3- and 4-position of phenethyl moiety in compound **10g** led to a slight decrease of inhibitory activity as observed in the case of compound **10p**. In this case, quinazolinone moiety established a π–π interaction with Phe300 (Fig. 5b).

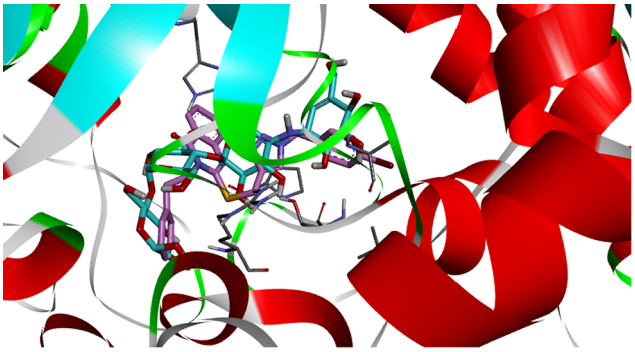


Fig. 3. Acarbose (cyan) and the most potent compound **10g** (pink) superimposed in the active site of *α*-glucosidase.

This compound formed a hydrogen bond and a hydrophobic interaction with Arg312 *via* 3-methoxy group and phenyl ring of phenethyl moiety. 4-Bromobenzyl group of compound **10p** showed two interactions with Glu304 and Pro309 through bromine and two interactions with His279 and Pro309 through phenyl ring (Fig. 5). Also, sulfur of this compound interacted with Phe157. Further studies on the binding energies of compounds **10g**, **10p**, and acarbose showed that compounds **10g** and **10p** have a lower free binding energy (−8.63 and −8.17 kcal/mol, respectively) than acarbose (−4.04 kcal/mol) and therefore bound more easily to *α*-glucosidase than acarbose. It also can explain the difference between the *α*-glucosidase inhibitory activity of compound **10g** with binding energy of −8.63 kcal/mol and its counterpart **10p** with binding energy of −8.17 kcal/mol.

3. Conclusion

In summary, a novel series of quinazolinone-1,2,3-triazole hybrids **10a-p** were designed and synthesized as new potent *α*-glucosidase inhibitors to develop efficient anti-diabetic agents. All synthesized compounds showed much better activity than the standard drug, acarbose. Compounds **10g** and **10p** were found to be the most active derivatives among the title compounds. Also, compound **10g** could inhibit *α*-glucosidase in a competitive manner. Furthermore, synthesized compounds **10a-p** showed no cytotoxicity against studied cancer and normal cell lines. Docking study of the most potent compounds **10g** and **10p** confirmed they have been well fitted in the active site of *α*-glucosidase *via* desirable interactions.

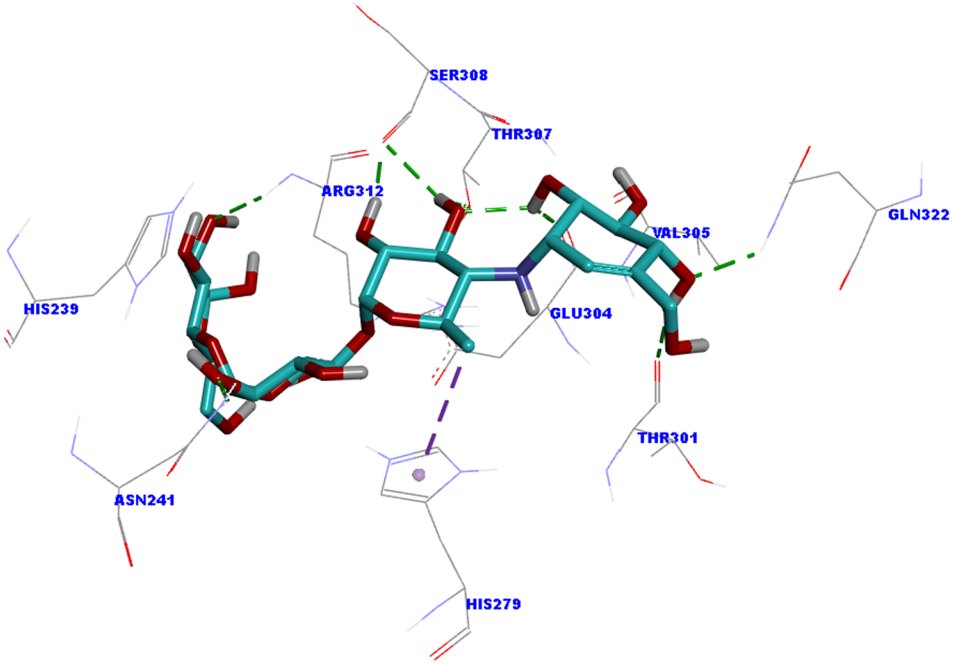


Fig. 4. Binding mode of acarbose in the active site of α-glucosidase.

4. Methods and materials

Melting points were determined on a Kofler hot stage apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker FT-500, using TMS as an internal standard. IR spectra were obtained on a Nicolet Magna FTIR 550 spectrophotometer (KBr disks). MS were recorded on an Agilent Technology (HP) mass spectrometer operating at an ionization potential of 70 eV. Elemental analysis was performed on an Elementar Analysensystem GmbH VarioEL CHNS mode.

*4.1. General procedure for the preparation of 2-amino-N-arylbenzamides **3***

A mixture of isatoic anhydride **1** (20 mmol) and amines **2** (20 mmol) in water (50 mL) was stirred for 2–3 h at room temperature. After completion of the reaction (checked by TLC, petroleum ether/ethyl acetate: 1/2), the precipitated product was filtered off affording 2-amino-*N*-arylbenzamide derivatives **3** which was used for the next reaction with no purification.

*4.2. General procedure for the preparation of thioxo-dihydroquinazolinones **5***

A mixture of compound **3** (2 mmol), carbon disulfide **4** (5 mmol), and potassium hydroxide (2 mmol) in EtOH (10 mL) was heated at reflux for 3–5 h. After completion of the reaction (checked by TLC, petroleum ether/ethyl acetate: 1/4), the reaction mixture was cooled down to room temperature, poured into ice-cold water, and the precipitated product was filtered off and recystilized from EtOH to give the corresponding thioxo-dihydroquinazolinone derivatives **5**.

*4.3. General procedure for the preparation of 2-(prop-2-ynylthio) quinazolin-4(3H)-one derivatives **7***

A mixture of compound **5** (1 mmol), propargyl bromide (1.2 mmol)

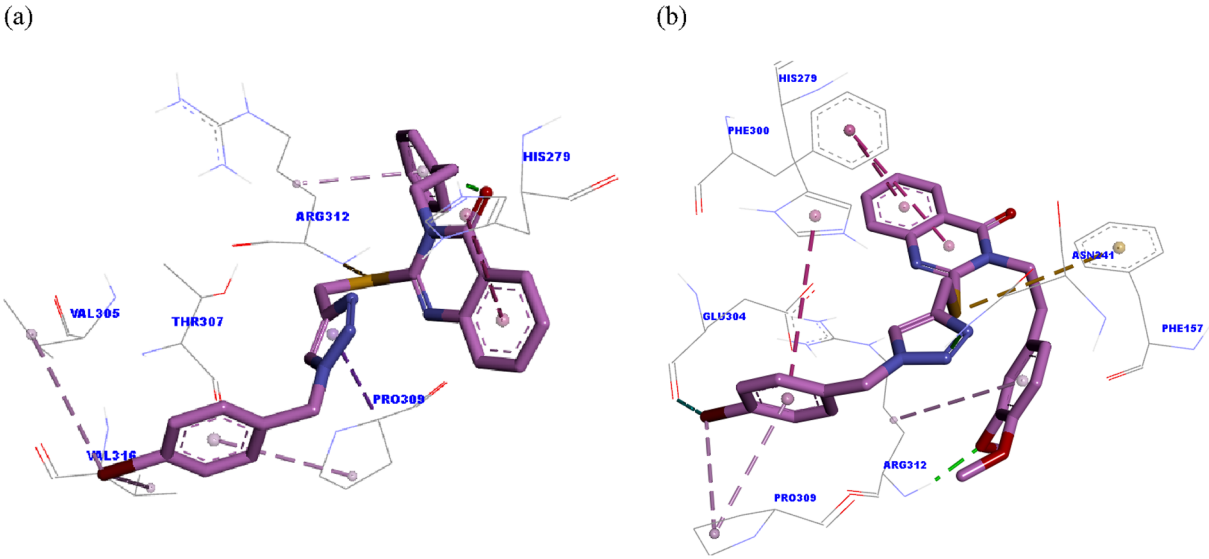


Fig. 5. Binding mode of the most potent compounds **10g** and **10p** in the α-glucosidase active site.

6, and potassium carbonate (1.5 mmol) in DMF (15 mL) was heated at 80 °C for 8 h. After that, the mixture was poured into ice-cold water, and the precipitated product was filtered off to obtain propargylated derivatives **7**.

4.4. General procedure for the synthesis of quinazolinone-1,2,3-triazole hybrids **10**

A solution of benzyl chloride/bromide **8** (1.1 mmol), sodium azide (0.9 mmol), and trimethylamine (1.3 mmol) in water (4 mL) and *tert*-butyl alcohol (4 mL) was stirred at room temperature for 30 min to give azide derivatives **9**. Then, compound **7** (1 mmol) and $CuSO_4{\cdot}5H_2O$ (7 mol%) were added to the reaction mixture and it was continued for 24 h. Upon completion of the reaction, monitored by TLC (petroleum ether/ethyl acetate: 1/4), the mixture was diluted with water, extracted with chloroform, and dried over anhydrous Na_2SO_4. After evaporation of solvent, the residue was recrystallized from ethyl acetate and petroleum ether to give pure product **10**.

4.4.1. 2-(((1-(4-Methylbenzyl)-1H-1,2,3-triazol-4-yl)methyl)thio)-3-phenethylquinazolin-4(3H)-one (**10a**)

Yield: 94%; mp = 121–126 °C; IR (KBr): 3050 (C−H), 2825 (C−H), 1675 (C=O), 1661, 1528 (C=N, C=C) cm^{-1}. ^{1}HNMR ($CDCl_3$, 500 MHz): δ = 2.47 (s, 3H, CH_3), 3.13–3.16 (m, 2H, CH_2), 4.38–4.42 (m, 2H, CH_2), 4.76 (s, 2H, CH_2), 5.57 (s, 2H, CH_2), 7.23–7.28 (m, 4H, H2′, H3′, H5′, H6′), 7.39–7.44 (m, 5H, Ph), 7.55 (t, $J_{H6\text{-}5,6\text{-}7}$ = 8.0 Hz, 1H, H6), 7.60–7.62 (m, 2H, H8, triazole), 7.82 (t, $J_{H7\text{-}6,7\text{-}8}$ = 8.0 Hz, 1H, H7), 8.37 (d, $J_{H5\text{-}6}$ = 8.0 Hz, 1H, H5) ppm. ^{13}CNMR ($CDCl_3$, 125 MHz): δ = 21.1, 26.8, 34.1, 46.2, 54.1, 119.3, 123.1, 125.7, 125.9, 126.8, 127.1, 128.1, 128.7, 128.9, 129.8, 131.5, 134.4, 137.6, 138.8, 144.0, 147.0, 155.9, 161.1 ppm. Anal. Calcd for $C_{27}H_{25}N_5OS$: C, 69.35; H, 5.39; N, 14.98. Found: C, 69.48; H, 5.21; N, 15.21.

4.4.2. 2-(((1-(3-Fluorobenzyl)-1H-1,2,3-triazol-4-yl)methyl)thio)-3-phenethylquinazolin-4(3H)-one (**10b**)

Yield: 73%; mp = 148–153 °C; IR (KBr): 3048 (C−H), 2829 (C−H), 1671 (C=O), 1660, 1550 (C=N, C=C) cm^{-1}. ^{1}HNMR ($CDCl_3$, 500 MHz): δ = 2.97 (t , $J_{CH2\text{-}CH2}$ = 7.5 Hz, 2H, CH_2), 4.22 (t, $J_{CH2\text{-}CH2}$ = 7.5 Hz, 2H, CH_2), 4.60 (s, 2H, CH_2), 5.42 (s, 2H, CH_2), 6.86 (d, $J_{H2'\text{-}3'}$ = 8.5 Hz, 1H, H2′), 6.93–6.97 (m, 2H, H4′, H5′), 7.21–7.25 (m, 6H, Ph, H3′), 7.37 (t, $J_{H6\text{-}5,6\text{-}7}$ = 7.0 Hz, 1H, H6), 7.46 (d, $J_{H8\text{-}7}$ = 7.0 Hz, 1H, H8), 7.51 (s, 1H, triazole), 7.65 (t, $J_{H7\text{-}6,7\text{-}8}$ = 7.0 Hz, 1H, H7), 8.18 (d, $J_{H5\text{-}6}$ = 7.0 Hz, 1H, H5) ppm. ^{13}CNMR ($CDCl_3$, 125 MHz): δ = 26.8, 34.1, 46.3, 53.6, 97.0, 115.1, 115.9, 119.4, 122.8, 123.5, 125.5, 126.0, 126.8, 127.1, 128.7, 128.9, 130.5, 134.5, 137.6, 144.5, 146.8, 155.4, 161.5, 162.2 ppm. Anal. Calcd for $C_{26}H_{22}FN_5OS$: C, 66.22; H, 4.70; N, 14.85. Found: C, 66.41; H, 4.52; N, 14.59.

4.4.3. 2-(((1-(2-Chlorobenzyl)-1H-1,2,3-triazol-4-yl)methyl)thio)-3-phenethylquinazolin-4(3H)-one (**10c**)

Yield: 88%; mp = 125–128 °C; IR (KBr): 3050 (C−H), 2829 (C−H), 1677 (C=O), 1668, 1552 (C=N, C=C) cm^{-1}. ^{1}HNMR ($CDCl_3$, 500 MHz): δ = 3.00–3.02 (m, 2H, CH_2), 4.25–4.27 (m, 2H, CH_2), 4.62 (s, 2H, CH_2), 5.60 (s, 2H, CH_2), 7.15–7.30 (m, 8H, Ph, H4′, H5′, H6′), 7.39–7.41 (m, 2H, H6, triazole), 7.51 (d, $J_{H8\text{-}7}$ = 6.0 Hz, 1H, H8), 7.65–7.69 (m, 2H, H7, H3′), 8.23 (d, $J_{H5\text{-}6}$ = 6.0 Hz, 1H, H5) ppm. ^{13}CNMR ($CDCl_3$, 125 MHz): δ = 26.9, 34.1, 46.2, 51.5, 96.1, 119.5, 123.3, 125.7, 125.9, 126.8, 127.1, 127.6, 128.7, 129.0, 129.9, 130.3, 130.4, 132.6, 134.4, 137.7, 144.2, 147.2, 155.7, 161.5 ppm. MS (*m/z*, %): 489 ($[M + 2]^{+\cdot}$, 5), 487 (M^+, 15), 334 (53), 281 (55), 249 (23), 230 (38), 207 (10), 178 (64), 162 (31), 125 (100), 104 (63), 89 (22), 77 (11). Anal. Calcd for $C_{26}H_{22}ClN_5OS$: C, 63.99; H, 4.54; N, 14.35. Found: C, 64.28; H, 4.38; N, 14.50.

4.4.4. 2-(((1-(3-Chlorobenzyl)-1H-1,2,3-triazol-4-yl)methyl)thio)-3-phenethylquinazolin-4(3H)-one (**10d**)

Yield: 89%; mp = 126–131 °C; IR (KBr): 3050 (C−H), 2829 (C−H), 1677 (C=O), 1668, 1552 (C=N, C=C) cm^{-1}. ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 3.02 (t, $J_{CH2\text{-}CH2}$ = 7.5 Hz, 2H, CH_2), 4.27 (t, $J_{CH2\text{-}CH2}$ = 7.5 Hz, 2H, CH_2), 4.64 (s, 2H, CH_2), 5.45 (s, 2H, CH_2), 7.09 (d, $J_{H6'\text{-}5'}$ = 7.5 Hz, 1H, H6′), 7.21–7.32 (m, 9H, Ph, H2′, H4′, H5′, triazole), 7.41 (t, $J_{H6\text{-}5,6\text{-}7}$ = 7.5 Hz, 1H, H6), 7.50 (d, $J_{H8\text{-}7}$ = 7.5 Hz, 1H, H8), 7.70 (t, $J_{H7\text{-}6,7\text{-}8}$ = 7.5 Hz, 1H, H7), 8.23 (d, $J_{H5\text{-}6}$ = 7.5 Hz, 1H, H5) ppm. ^{13}CNMR ($CDCl_3$, 125 MHz): δ = 26.9, 34.1, 46.3, 53.5, 96.1, 119.6, 123.4, 125.6, 125.8, 126.0, 126.8, 127.2, 127.8, 128.1, 128.7, 129.0, 129.0, 130.4, 134.5, 137.6, 144.1, 147.2, 155.6, 168.5 ppm. MS (*m/z*, %): 489 ($[M + 2]^{+\cdot}$, 5), 487 (M^+, 15), 334 (50), 281 (84), 249 (30), 230 (44), 178 (76), 162 (38), 125 (100), 104 (86), 89 (24), 77 (14). Anal. Calcd for $C_{26}H_{22}ClN_5OS$: C, 63.99; H, 4.54; N, 14.35. Found: C, 64.32; H, 4.78; N, 14.15.

4.4.5. 2-(((1-(4-Chlorobenzyl)-1H-1,2,3-triazol-4-yl)methyl)thio)-3-phenethylquinazolin-4(3H)-one (**10e**)

Yield: 91%; mp = 129–132 °C; IR (KBr): 3050 (C−H), 2828 (C−H), 1672 (C=O), 1665, 1552 (C=N, C=C) cm^{-1}. ^{1}HNMR ($CDCl_3$, 500 MHz): δ = 3.01–3.03 (m, 2H, CH_2), 4.26–4.28 (m, 2H, CH_2), 4.62 (s, 2H, CH_2), 5.45 (s, 2H, CH_2), 7.15 (d, $J_{H2',6'\text{-}3',5'}$ = 7.0 Hz, 2H, H2′, H6′), 7.26–7.31 (m, 7H, Ph, H3′, H5′), 7.42–7.50 (m, 3H, H6, H8, triazole), 7.70 (t, $J_{H7\text{-}6,7\text{-}8}$ = 7.0 Hz, 1H, H7), 8.24 (d, $J_{5\text{-}6}$ = 7.0 Hz, 1H, H5) ppm. ^{13}CNMR ($CDCl_3$, 125 MHz): δ = 26.8, 34.1, 46.2, 53.4, 96.1, 119.2, 122.8, 123.9, 125.6, 126.0, 126.8, 127.1, 128.7, 128.9, 129.4, 133.0, 134.4, 137.6, 144.3, 147.1, 155.3, 161.4 ppm. Anal. Calcd for $C_{26}H_{22}ClN_5OS$: C, 63.99; H, 4.54; N, 14.35. Found: C, 63.78; H, 4.21; N, 14.24.

4.4.6. 2-(((1-(2-Bromobenzyl)-1H-1,2,3-triazol-4-yl)methyl)thio)-3-phenethylquinazolin-4(3H)-one (**10f**)

Yield: 86%; mp = 130–133 °C; IR (KBr): 3051 (C−H), 2829 (C−H), 1675 (C=O), 1665, 1550 (C=N, C=C) cm^{-1}. ^{1}HNMR ($CDCl_3$, 500 MHz): δ = 3.01 (t, $J_{CH2\text{-}CH2}$ = 8.0 Hz, 2H, CH_2), 4.27 (t, $J_{CH2\text{-}CH2}$ = 8.0 Hz, 2H, CH_2), 4.62 (s, 2H, CH_2), 5.60 (s, 2H, CH_2), 7.12 (d, $J_{H6'\text{-}5'}$ = 7.5 Hz, 1H, H6′), 7.19–7.30 (m, 7H, Ph, H4′, H5′), 7.41 (t, $J_{H6\text{-}5,6\text{-}7}$ = 7.5 Hz, 1H, H6), 7.50 (d, $J_{H8\text{-}7}$ = 7.5 Hz, 1H, H8), 7.56 (d, $J_{H3'\text{-}4'}$ = 7.5 Hz, 1H, H3′), 7.66–7.70 (m, 2H, H7, triazole), 8.23 (d, $J_{5\text{-}6}$ = 7.5 Hz, 1H, H5) ppm. ^{13}CNMR ($CDCl_3$, 125 MHz): δ = 26.9, 34.1, 46.2, 53.9, 96.1, 119.1 123.4, 125.8, 126.0, 126.8, 127.1, 127.3, 128.2, 128.7, 129.0, 129.1, 130.4, 133.2, 134.4, 137.6, 144.0, 147.1, 155.8, 161.2 ppm. Anal. Calcd for $C_{26}H_{22}BrN_5OS$: C, 58.65; H, 4.16; N, 13.15. Found: C, 58.48; H, 4.31; N, 13.34.

4.4.7. 2-(((1-(4-Bromobenzyl)-1H-1,2,3-triazol-4-yl)methyl)thio)-3-phenethylquinazolin-4(3H)-one (**10g**)

Yield: 89%; mp = 131–133 °C; IR (KBr): 3050 (C−H), 2829 (C−H), 1672 (C=O), 1669, 1578 (C=N, C=C) cm^{-1}. ^{1}H NMR ($CDCl_3$, 500 M Hz): δ = 3.02–3.04 (m, 2H, CH_2), 4.27–4.29 (m, 2H, CH_2), 4.61 (s, 2H, CH_2), 5.43 (s, 2H, CH_2), 7.08 (d, $J_{H2',6'\text{-}3',5'}$ = 8.0 Hz, 2H, H2′, H6′), 7.24–7.32 (m, 5H, Ph), 7.41–7.46 (m, 5H, H6, H8, H3′, H5′, triazole), 7.70 (t, $J_{H7\text{-}6,7\text{-}8}$ = 7.5 Hz, 1H, H7), 8.24 (d, $J_{H5\text{-}6}$ = 7.5 Hz, 1H, H5) ppm. ^{13}CNMR ($CDCl_3$, 125 MHz): δ = 26.8, 34.1, 46.2, 53.5, 96.0, 119.5, 123.0, 125.7, 126.0, 126.8, 127.1, 128.7, 128.9, 129.7, 132.3, 133.4, 134.4, 137.7, 140.2, 147.1, 155.5, 161.4 ppm. Anal. Calcd for $C_{26}H_{22}BrN_5OS$: C, 58.65; H, 4.16; N, 13.15. Found: C, 58.47; H, 4.40; N, 13.28.

4.4.8. 3-(3,4-Dimethoxyphenethyl)-2-(((1-(4-methylbenzyl)-1H-1,2,3-triazol-4-yl)methyl)thio) quinazolin-4(3H)-one (**10h**)

Yield: 90%; mp = 135–138 °C; IR (KBr): 3055 (C−H), 2829 (C−H), 1678 (C=O), 1663, 1558 (C=N, C=C) cm^{-1}. ^{1}HNMR ($CDCl_3$, 500 MHz): δ = 2.34 (s, 3H, CH_3), 2.96–2.98 (m, 2H, CH_2), 3.83 (s, 3H, OMe), 3.86 (s, 3H, OMe), 4.26–4.28 (m, 2H, CH_2), 4.60 (s, 2H, CH_2),

5.42 (s, 2H, CH_2), 6.79–6.83 (m, 2H, H2″, H5″), 6.86 (d, $J_{H6''-5''}$ = 8.0 Hz, 1H, H6″), 7.09–7.13 (m, 5H, H2′, H3′, H5′, H6′, triazole), 7.41 (t, $J_{H6-5,6-7}$ = 7.5 Hz, 1H, H6), 7.45 (d, J_{H8-7} = 7.5 Hz, 1H, H8), 7.68 (t, $J_{H7-6,7-8}$ = 7.5 Hz, 1H, H7), 8.23 (d, J_{H5-6} = 7.5 Hz, 1H, H5) ppm. ^{13}CNMR ($CDCl_3$, 125 MHz): δ = 21.2, 26.9, 33.6, 46.4, 54.0, 55.8, 55.9, 96.0, 111.4, 112.1, 119.4, 121.0, 125.7, 125.9, 127.0, 128.1, 129.7, 130.2, 131.4, 134.4, 138.7, 144.5, 147.1, 147.9, 149.0, 155.6, 161.5 ppm. Anal. Calcd for $C_{29}H_{29}N_5O_3S$: C, 66.01; H, 5.54; N, 13.27. Found: C, 66.31; H, 5.38; N, 13.51.

*4.4.9. 3-(3,4-Dimethoxyphenethyl)-2-(((1-(3-fluorobenzyl)-1H-1,2,3-triazol-4-yl)methyl)thio) quinazolin-4(3H)-one (**10i**)*

Yield: 70%; mp = 150–151 °C; IR (KBr): 3050 (C—H), 2829 (C—H), 1677 (C=O), 1660, 1556 (C=N, C=C) cm^{-1}. ^{1}HNMR ($CDCl_3$, 500 MHz): δ = 2.98–3.00 (m, 2H, CH_2), 3.82 (s, 3H, OMe), 3.85 (s, 3H, OMe), 4.28–4.29 (m, 2H, CH_2), 4.60 (s, 2H, CH_2), 5.48 (s, 2H, CH_2), 6.77–6.80 (m, 3H, H2″, H5″, H6″), 6.88 (d, $J_{H6'-5'}$ = 7.0 Hz, H6′), 6.89 (d, $J_{H2'-F}$ = 7.0 Hz, H2′), 6.96–7.03 (m, 2H, H5′, triazole), 7.28 (t, $J_{H4'-5',4'-F}$ = 7.0 Hz, 1H, H4′), 7.41 (t, $J_{H6-5,6-7}$ = 7.5 Hz, 1H, H6),7.45 (d, J_{H8-7} = 7.5 Hz, 1H, H8), 7.69 (t, $J_{H7-6,7-8}$ = 7.5 Hz, 1H, H7), 8.23 (d, J_{H5-6} = 7.5 Hz, 1H, H5) ppm. ^{13}CNMR ($CDCl_3$, 125 MHz): δ = 26.1, 33.6, 46.4, 52.5, 55.9, 56.0, 96.1, 111.5, 112.2, 115.0 (d, J = 21.2 Hz), 115.8 (d, J = 20.0 Hz), 119.5, 121.1, 123.5, 125.7, 125.9, 127.1, 130.2, 130.7 (d, J = 8.7 Hz), 134.4, 136.9, 145.5, 147.2, 147.9, 149.0, 155.5, 161.4, 162.9 (d, J = 246.2 Hz) ppm. MS (*m/z*, %): 531 (M^+, 15), 341 (28), 164 (100), 149 (17), 109 (62). Anal. Calcd for $C_{28}H_{26}FN_5O_3S$: C, 63.26; H, 4.93; N, 13.17. Found: C, 63.51; H, 4.71; N, 13.29.

*4.4.10. 3-(3,4-Dimethoxyphenethyl)-2-(((1-(4-fluorobenzyl)-1H-1,2,3-triazol-4-yl)methyl)thio) quinazolin-4(3H)-one (**10j**)*

Yield: 73%; mp = 151–153 °C; IR (KBr): 3054 (C—H), 2828 (C—H), 1675 (C=O), 1662, 1558 (C=N, C=C) cm^{-1}. ^{1}HNMR ($CDCl_3$, 500 MHz): δ = 2.97–2.99 (m, 2H, CH_2), 3.82 (s, 3H, OMe), 3.85 (s, 3H, OMe), 4.27–4.29 (m, 2H, CH_2), 4.59 (s, 2H, CH_2), 5.44 (s, 2H, CH_2), 6.78–6.81 (m, 2H, H2″, H5″), 6.85 (d, $J_{H6''-5''}$ = 7.5 Hz, 1H, H6″), 7.00 (t, $J_{H3',5'-2',6'-F}$ = 7.5 Hz, 2H, H3′, H5′), 7.17–7.22 (m, 3H, H2′, H6′, triazole), 7.40–7.44 (m, 2H, H6, H8), 7.68 (t, $J_{H7-6,7-8}$ = 7.5 Hz, 1H, H7), 8.23 (d, J_{H5-6} = 7.5 Hz, 1H, H5) ppm. ^{13}CNMR ($CDCl_3$, 125 MHz): δ = 27.5, 33.6, 46.4, 53.5, 55.9, 56.0, 96.1, 111.5, 112.2, 116.0 (d, J = 22.5 Hz), 119.4, 121.0, 125.7, 126.0, 127.1, 130.0, 130.1 (d, J = 8.0 Hz), 134.4, 135.2, 144.5, 147.1, 147.9, 149.0, 155.7, 161.4, 162.5 (d, J = 245. Hz) ppm. Anal. Calcd for $C_{28}H_{26}FN_5O_3S$: C, 63.26; H, 4.93; N, 13.17. Found: C, 63.41; H, 5.24; N, 12.88.

*4.4.11. 2-(((1-(2-Chlorobenzyl)-1H-1,2,3-triazol-4-yl)methyl)thio)-3-(3,4-dimethoxyphenethyl) quinazolin-4(3H)-one (**10k**)*

Yield: 80%; mp = 135–139 °C; IR (KBr): 3050 (C—H), 2828 (C—H), 1672 (C=O), 1665, 1558 (C=N, C=C) cm^{-1}. ^{1}HNMR ($CDCl_3$, 500 MHz): δ = 2.96 (t, $J_{CH2-CH2}$ = 7.0 Hz, 2H, CH_2), 3.83 (s, 3H, OMe), 3.85 (s, 3H, OMe), 4.24–4.26 (m, 2H, CH_2), 4.62 (s, 2H, CH_2), 5.61 (s, 2H, CH_2), 6.77–6.80 (m, 3H, H6′, H2″, H5″), 6.84 (d, $J_{H6''-5''}$ = 7.5 Hz, 1H, H6″), 7.15 (d, $J_{H3'-4'}$ = 7.0 Hz, 1H, H3′), 7.20 (t, $J_{H4'-3',4'-5'}$ = 7.0 Hz, 1H, H4′), 7.27 (t, $J_{H5'-4',5'-6'}$ = 7.0 Hz, 1H, H5′), 7.37–7.43 (m, 2H, H6, triazole), 7.50 (d, J_{H8-7} = 7.5 Hz, 1H, H8), 7.69 (t, $J_{H7-6,7-8}$ = 7.5 Hz, 1H, H7), 8.23 (d, J_{H5-6} = 7.5 Hz, 1H, H5) ppm. ^{13}CNMR ($CDCl_3$, 125 MHz): δ = 26.8, 33.6, 46.4, 51.5, 55.9, 56.0, 96.1, 111.5, 112.1, 119.6, 121.0, 125.7, 125.9, 127.1, 127.6, 129.9, 130.3, 130.4, 132.4, 134.4, 144.2, 147.1, 147.8, 149.1, 151.9, 154.1, 155.7, 161.4 ppm. Anal. Calcd for $C_{28}H_{26}ClN_5O_3S$: C, 61.36; H, 4.78; N, 12.78. Found: C, 61.58; H, 4.59; N, 12.51.

*4.4.12. 2-(((1-(3-Chlorobenzyl)-1H-1,2,3-triazol-4-yl)methyl)thio)-3-(3,4-dimethoxyphenethyl) quinazolin-4(3H)-one (**10l**)*

Yield: 76%; mp = 138–140 °C; IR (KBr): 3050 (C—H), 2828 (C—H), 1675 (C=O), 1663, 1559 (C=N, C=C) cm^{-1}. ^{1}HNMR ($CDCl_3$, 500 MHz): δ = 3.03–3.05 (m, 2H, CH_2), 3.88 (s, 3H, OMe), 3.91 (s, 3H, OMe), 4.33–4.35 (m, 2H, CH_2), 4.68 (s, 2H, CH_2), 5.52 (s, 2H, CH_2), 6.84–6.87 (m, 2H, H2″, H5″), 6.92 (d, $J_{H6''-5''}$ = 7.5 Hz, 1H, H6″), 7.14 (d, $J_{H6'-5'}$ = 7.0 Hz, 1H, H6′), 7.26–7.36 (m, 4H, H2′, H4′, H5′, triazole), 7.47 (t, $J_{H6-5,6-7}$ = 7.5 Hz, 1H, H6), 7.53 (d, J_{H8-7} = 7.5 Hz, 1H, H8), 7.76 (t, $J_{H7-6,7-8}$ = 7.5 Hz, 1H, H7), 8.29 (d, J_{H5-6} = 7.5 Hz, 1H, H5) ppm. ^{13}CNMR ($CDCl_3$, 125 MHz): δ = 26.9, 33.6, 46.4, 50.9, 54.0, 55.9, 96.0, 111.5, 112.1, 119.4, 121.1, 125.7, 125.9, 126.1, 127.0, 128.1, 129.0, 130.2, 130.3, 134.5, 135.0, 136.4, 147.1, 147.9, 149.0, 151.8, 155.5, 161.4 ppm. Anal. Calcd for $C_{28}H_{26}ClN_5O_3S$: C, 61.36; H, 4.78; N, 12.78. Found: C, 61.60; H, 4.87; N, 12.84.

*4.4.13. 2-(((1-(4-Chlorobenzyl)-1H-1,2,3-triazol-4-yl)methyl)thio)-3-(3,4-dimethoxyphenethyl) quinazolin-4(3H)-one (**10m**)*

Yield: 84%; mp = 137–140 °C; IR (KBr): 3058 (C—H), 2828 (C—H), 1675 (C=O), 1667, 1561 (C=N, C=C) cm^{-1}. ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 2.96–2.98 (m, 2H, CH_2), 3.83 (s, 3H, OMe), 3.86 (s, 3H, OMe), 4.26–4.28 (m, 2H, CH_2), 4.60 (s, 2H, CH_2), 5.45 (s, 2H, CH_2), 6.78–6.81 (m, 2H, H2″, H5″), 6.85 (d, $J_{H6''-5''}$ = 8.0 Hz, 1H, H6″), 7.14 (d, $J_{H2',6'-3',5'}$ = 7.5 Hz, 2H, H2′, H6′), 7.29 (d, $J_{H3',5'-2',6'}$ = 7.5 Hz, 2H, H3′, H5′), 7.40–7.44 (m, 3H, H6, H8, triazole), 7.70 (t, J_{H7-8} = 7.5 Hz, 1H, H7), 8.24 (d, J_{H8-7} = 7.5 Hz, 1H, H8) ppm. ^{13}CNMR ($CDCl_3$, 125 MHz): δ = 26.9, 33.6, 46.4, 53.5, 55.8, 55.9, 96.0, 111.5, 112.1, 119.4, 121.0, 125.7, 126.0, 127.1, 129.3, 129.4, 130.2, 132.9, 134.4, 135.8, 145.8, 147.1, 147.9, 149.0, 155.5, 161.5 ppm. Anal. Calcd for $C_{28}H_{26}ClN_5O_3S$: C, 61.36; H, 4.78; N, 12.78. Found: C, 61.46; H, 4.49; N, 12.51.

*4.4.14. 2-(((1-(2-Bromobenzyl)-1H-1,2,3-triazol-4-yl)methyl)thio)-3-(3,4-dimethoxylphenethyl) quinazolin-4(3H)-one (**10n**)*

Yield: 84%; mp = 142–145 °C; IR (KBr): 3050 (C—H), 2829 (C—H), 1675 (C=O), 1663, 1585 (C=N, C=C) cm^{-1}. ^{1}HNMR ($CDCl_3$, 500 MHz): δ = 2.96 (t, $J_{CH2-CH2}$ = 8.0 Hz, 2H, CH_2), 3.83 (s, 3H, OMe), 3.85 (s, 3H, OMe), 4.25 (t, $J_{CH2-CH2}$ = 8.0 Hz, 2H, CH_2), 4.62 (s, 2H, CH_2), 5.60 (s, 2H, CH_2), 6.79 (d, $J_{5''-6''}$ = 8.5 Hz, 1H, H5″), 6.81 (s, 1H, H2″), 6.85 (d, $J_{H6''-5''}$ = 8.5 Hz, 1H, H6″), 7.13 (d, $J_{H6'-5'}$ = 7.0 Hz, 1H, H6′), 7.19 (t, $J_{H4'-3',4'-5'}$ = 7.0 Hz, 1H, H4′), 7.24 (t, $J_{H5'-4',5'-6'}$ = 7.0 Hz, 1H, H5′),7.41 (t, $J_{H6-5,6-7}$ = 7.5 Hz, 1H, H6), 7.51 (d, J_{H8-7} = 7.5 Hz, 1H, H8), 7.55 (d, $J_{H3'-4'}$ = 7.5 Hz, 1H, H3′), 7.66 (s, 1H, triazole), 7.69 (t, $J_{H7-6,7-8}$ = 7.5 Hz, 1H, H7), 8.23 (d, J_{H5-6} = 7.5 Hz, 1H, H5) ppm. ^{13}CNMR (CDCl3, 125 MHz): δ = 26.8, 33.6, 46.4, 53.9, 55.9, 56.0, 97.5, 111.5, 112.1, 119.5, 121.0, 123.4, 123.5, 125.7, 125.9, 127.1, 128.2, 130.2, 130.4, 133.2, 134.0, 134.4,144.1, 147.1, 147.9, 149.0, 155.6, 161.4 ppm. Anal. Calcd for $C_{28}H_{26}BrN_5O_3S$: C, 56.76; H, 4.42; N, 11.82. Found: C, 56.58; H, 4.21; N, 12.10.

*4.4.15. 2-(((1-(3-Bromobenzyl)-1H-1,2,3-triazol-4-yl)methyl)thio)-3-(3,4-dimethoxyphenethyl) quinazolin-4(3H)-one (**10o**)*

Yield: 86%; mp = 144–148 °C; IR (KBr): 3050 (C—H), 2828 (C—H), 1671 (C=O), 1666, 1566 (C=N, C=C) cm^{-1}. ^{1}HNMR ($CDCl_3$, 500 MHz): δ = 2.97–2.99 (m, 2H, CH_2), 3.82 (s, 3H, OMe), 3.85 (s, 3H, OMe), 4.26–4.28 (m, 2H, CH_2), 4.61 (s, 2H, CH_2), 5.46 (s, 2H, CH_2), 6.77–6.80 (m, 2H, H2″, H5″), 6.85 (d, $J_{H6''-5''}$ = 7.0, 1H, H6″), 7.13 (d, $J_{H6'-5'}$ = 7.0 Hz, 1H, H6′), 7.19 (t, $J_{H5'-4',5'-6'}$ = 7.0 Hz, 1H, H5′), 7.37–7.48 (m, 5H, H6, H8, H2′, H4′, triazole), 7.70 (t, $J_{H7-6,7-8}$ = 7.5 Hz, 1H, H7), 8.23 (d, J_{H5-6} = 7.5 Hz, 1H, H5) ppm. ^{13}CNMR ($CDCl_3$, 125 MHz): δ = 26.9, 33.6, 46.4, 52.5,55.8, 55.9, 96.1, 115.5, 112.2, 119.5, 121.1, 123.1,125.7, 126.0, 126.5, 127.1, 130.2, 130.6,131.0, 131.9, 134.5, 136.7, 146.0, 147.1, 147.9, 149.0, 155.6, 161.4 ppm. Anal. Calcd for $C_{28}H_{26}BrN_5O_3S$: C, 56.76; H, 4.42; N, 11.82. Found: C, 56.81; H, 4.27; N, 11.67.

*4.4.16. 2-(((1-(4-Bromobenzyl)-1H-1,2,3-triazol-4-yl)methyl)thio)-3-(3,4-dimethoxyphenethyl) quinazolin-4(3H)-one (**10p**)*

Yield: 84%; mp = 144–146 °C; IR (KBr): 3052 (C—H), 2828 (C—H), 1672 (C=O), 1680, 1556 (C=N, C=C) cm^{-1}. ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 2.96–2.98 (m, 2H, CH_2), 3.82 (s, 3H, OMe), 3.85 (s, 3H,

OMe), 4.25–4.27 (m, 2H, CH_2), 4.59 (s, 2H, CH_2), 5.43 (s, 2H, CH_2), 6.77 (s, 1H, H2″), 6.80 (d, $J_{H5''-6''}$ = 7.5 Hz, 1H, H5″), 6.84 (d, $J_{H6''-5''}$ = 7.5 Hz, 1H, H6″), 7.08 (d, $J_{H2',6-3',5'}$ = 8.0, 2H, H2′, H6′), 7.41–7.45 (m, 5H, H6, H8, H3′, H5′, triazole), 7.70 (t, $J_{H7-6,7-8}$ = 7.5 Hz, 1H, H7), 8.24 (d, J_{H5-6} = 7.5 Hz, 1H, H5) ppm. ^{13}CNMR ($CDCl_3$, 125 MHz): δ = 26.7, 33.6, 46.4, 55.7, 55.9, 96.1, 111.5, 112.2, 119.5, 121.1, 123.0, 125.7, 126.0, 127.1, 129.7, 130.2, 132.3, 133.5, 134.4, 144.2, 147.1, 147.9, 149.0, 155.6, 161.4 ppm. Anal. Calcd for $C_{28}H_{26}BrN_5O_3S$: C, 56.76; H, 4.42; N, 11.82. Found: C, 56.91; H, 4.65; N, 11.67.

4.5. In vitro α-glucosidase inhibition assay

α-Glucosidase (Saccharomyces cerevisiae, EC3.2.1.20, 20 U/mg) and substrate (*p*-nitrophenyl glucopyranoside) were purchased from Sigma-Aldrich. Desired concentrations of enzyme were prepared by potassium phosphate buffer (pH 6.8, 50 mM), and the target compounds **10a-p** were dissolved in DMSO (10% final concentration). The enzyme solution (20 μL), different concentrations of compounds **10a-p** (20 μL), and potassium phosphate buffer (135 μL) were added to the 96-well plate and incubated at 37 °C for 10 min. Then, *p*-nitrophenyl glucopyranoside as substrate (25 μL, 4 mM) was added to each well and allowed to be incubated at 37 °C for 20 min. Finally, the change in the absorbance was measured at 405 nm by using spectrophotometer (Gen5, Power wave xs2, BioTek, America). DMSO and acarbose were used as the control and standard inhibitor, respectively. The percentage of inhibition for target compounds, control, and the standard inhibitor was calculated by using the following formula:

$$\%\,\text{Inhibition} = [(\text{Abs control} - \text{Abs sample})/\text{Abs control}] \times 100$$

IC_{50} values of tested compounds were obtained from the nonlinear regression curve using the Logit method.

4.6. Kinetic study

The enzyme solution (1 U/mL, 20 μL) was incubated with different concentrations of 0, 140, 160, and 180 μM of the most potent compound **10g** (20 μL) for 15 min at 30 °C. The reaction was then initiated by adding various concentrations of substrate (*p*-nitrophenyl glucopyranoside, 1–4 mM). Then, change in the absorbance was determined for 20 min at 405 nm by using spectrophotometer (Gen5, Power wave xs2, BioTek, America) [25].

4.7. In vitro cytotoxicity assay

Evaluation of cytotoxic effects of the quinazolinone-1,2,3-triazole hybrids **10a-p** was performed exactly based on the literature [15].

4.8. Docking study

Building the homology model of α-glucosidase and docking of the most potent compounds **10g** and **10p** in this enzyme were performed by Auto dock Tools, using previously described method [26].

Conflict of interest

The authors have declared no conflict of interest.

Acknowledgment

This work was supported by Research Council of Tehran University of Medical Sciences with grant No. 97-02-96-39641.

References

[1] M. Saeedi, A. Hadjiakhondi, S.M. Nabavi, A. Manayi, Heterocyclic compounds: effective α-amylase and α-glucosidase inhibitors, Curr. Top. Med. Chem. 17 (2016) 428–440.
[2] A.J. Hirsh, S.Y. Yao, J.D. Young, C.I. Cheeseman, Inhibition of glucose absorption in the rat jejunum: a novel action of alpha-D-glucosidase inhibitors, Gastroenterology 113 (1997) 205–211.
[3] S.R. Joshi, E. Standl, N. Tong, P. Shah, S. Kalra, R. Rathod, Therapeutic potential of α-glucosidase inhibitors in type 2 diabetes mellitus: an evidence-based review, Expert Opin. Pharmacother. 16 (2015) 1959–1981.
[4] P. Hollander, Safety profile of acarbose, an α-glucosidase inhibitor, Drugs 44 (Suppl 3) (1992) 47–53.
[5] M. Ghasemian, M. Mahdavi, P. Zare, M.A.H. Feizi, Spiroquinazolinone-induced cytotoxicity and apoptosis in K562 human leukemia cells: alteration in expression levels of Bcl-2 and Bax, J. Toxicol. Sci. 40 (2015) 115–126.
[6] F. Khajoee Nejad, M. Khosravan, S.Y. Ebrahimipour, F. Bisceglie, A mixed-ligand quinazoline-based Ni (II) Schiff base complex: Synthesis, characterization, crystal structure, antimicrobial investigation and catalytic activity for the synthesis of 2*H*–indazolo[2,1-*b*] phthalazine-triones, Appl. Organometal. Chem. 32 (2018) e3907.
[7] M.S. Malamas, J. Millen, Quinazolineacetic acids and related analogs as aldose reductase inhibitors, J. Med. Chem. 34 (1991) 1492–1503.
[8] T. Mohamed, P.P.N. Rao, 2,4-Disubstituted quinazolines as amyloid-β aggregation inhibitors with dual cholinesterase inhibition and antioxidant properties: development and structure-activity relationship (SAR) studies, Eur. J. Med. Chem. 126 (2017) 823–843.
[9] C. Balakumar, P. Lamba, D.P. Kishore, B.L. Narayana, K.V. Rao, K. Rajwinder, A.R. Rao, B. Shireesha, B. Narsaiah, Synthesis, anti-inflammatory evaluation and docking studies of some new fluorinated fused quinazolines, Eur. J. Med. Chem. 45 (2012) 4904–4913.
[10] S.T. Al-Rashood, I.A. Aboldahab, M.N. Nagi, L.A. Abouzeid, A.A. Abdel-Aziz, S.G. Abdel-hamide, K.M. Youssef, A.M. Al-Obaid, H.I. El-Subbagh, Synthesis, dihydrofolate reductase inhibition, antitumor testing, and molecular modeling study of some new 4 (3*H*)-quinazolinone analogs, Bioorg. Med. Chem. 14 (2006) 8608–8621.
[11] A. Gangjee, O.O. Adair, M. Pagley, S.F. Queener, N9-substituted 2, 4-diaminoquinazolines: synthesis and biological evaluation of lipophilic inhibitors of *Pneumocystis carinii* and *Toxoplasma gondii* dihydrofolate reductase, J. Med. Chem. 51 (2008) 6195–6200.
[12] V. Gurram, R. Garlapati, C. Thulluri, N. Madala, K.S. Kasani, P.K. Machiraju, R. Doddapalla, U. Addepally, R. Gundla, B. Patro, N. Pottabathini, Design, synthesis, and biological evaluation of quinazoline derivatives as α-glucosidase inhibitors, Med. Chem. Res. 24 (2015) 2227–2237.
[13] K. Javaid, S.M. Saad, S. Rasheed, S.T. Moin, N. Syed, I. Fatima, U. Salar, K.M. Khan, S. Perveen, M.I. Choudhary, 2-Arylquinazolin-4(3*H*)-ones: a new class of α-glucosidase inhibitors, Bioorg. Med. Chem. 23 (2015) 7417–7421.
[14] M. Wei, W.M. Chai, R. Wang, Q. Yang, Z. Deng, Y. Peng, Quinazolinone derivatives: synthesis and comparison of inhibitory mechanisms on α-glucosidase, Bioorg. Med. Chem. 25 (2017) 1303–1308.
[15] M. Mohammadi-Khanaposhtani, M. Safavi, R. Sabourian, M. Mahdavi, M. Pordeli, M. Saeedi, S.K. Ardestani, A. Foroumadi, A. Shafiee, T. Akbarzadeh, Design, synthesis, *in vitro* cytotoxic activity evaluation, and apoptosis-induction study of new 9(10*H*)-acridinone-1,2,3-triazoles, Mol. Divers. 19 (2015) 787–795.
[16] M. Saeedi, S. Ansari, M. Mahdavi, R. Sabourian, T. Akbarzadeh, A. Foroumadi, A. Shafiee, Synthesis of novel 1,2,3-triazole-dihydro[3,2-*c*]chromenones as acetylcholinesterase inhibitors, Synth. Commun. 45 (2015) 2311–2318.
[17] W. Tan, Q. Li, W. Li, F. Dong, Z. Guo, Synthesis and antioxidant property of novel 1,2,3-triazole-linked starch derivatives via 'click chemistry', Int. J. Biol. Macromol. 82 (2016) 404–410.
[18] A. Ayati, S. Emami, A. Foroumadi, The importance of triazole scaffold in the development of anticonvulsant agents, Eur. J. Med. Chem. 109 (2016) 380–392.
[19] F. Jabeen, S.A. Shehzadi, M.Q. Fatmi, S. Shaheen, L. Iqbal, N. Afza, S.S. Panda, F.L. Ansari, Synthesis, in vitro and computational studies of 1,4-disubstituted 1,2,3-triazoles as potential α-glucosidase inhibitors, Bioorg. Med. Chem. Lett. 26 (2016) 1029–1038.
[20] Y. Chinthala, A.K. Domatti, A. Sarfaraz, S.P. Singh, N.K. Arigari, N. Gupta, S.K. Satya, J.K. Kumar, F. Khan, A.K. Tiwari, G. Paramjit, Synthesis, biological evaluation and molecular modeling studies of some novel thiazolidinediones with triazole ring, Eur. J. Med. Chem. 70 (2013) 308–314.
[21] S. Iqbal, M.A. Khan, K. Javaid, R. Sadiq, S. Fazal-Ur-Rehman, M.I. Choudhary, F.Z. Basha, New carbazole linked 1,2,3-triazoles as highly potent non-sugar α-glucosidase inhibitors, Bioorg. Chem. 74 (2017) 72–81.
[22] G. Wang, Z. Peng, J. Wang, X. Li, J. Li, Synthesis, *in vitro* evaluation and molecular docking studies of novel triazine-triazole derivatives as potential α-glucosidase inhibitors, Eur. J. Med. Chem. 125 (2017) 423–429.
[23] C. Viegas-Junior, A. Danuello, V. da Silva Bolzani, E.J. Barreiro, C.A.M. Fraga, Molecular hybridization: a useful tool in the design of new drug prototypes, Curr. Med. Chem. 14 (2007) 1829–1852.
[24] H. Nikookar, M. Mohammadi-Khanaposhtani, S. Imanparast, M.A. Faramarzi, P.R. Ranjbar, M. Mahdavi, B. Larijani, Design, synthesis and in vitro α-glucosidase inhibition of novel dihydropyrano [3,2-*c*]quinoline derivatives as potential anti-diabetic agents, Bioorg. Chem. 77 (2018) 280–286.
[25] M. Mohammadi-Khanaposhtani, S. Rezaei, R. Khalifeh, S. Imanparast, M.A. Faramarzi, S. Bahadorikhalili, M. Safavi, F. Bandarian, E.N. Esfahani, M. Mahdavi, B. Larijani, Design, synthesis, docking study, α-glucosidase inhibition, and cytotoxic activities of acridine linked to thioacetamides as novel agents in treatment of type 2 diabetes, Bioorg. Chem. 80 (2018) 288–295.
[26] M. Adib, F. Peytam, M. Rahmanian-Jazi, S. Mahernia, H.R. Bijanzadeh, M. Jahani,

M. Mohammadi-Khanaposhtani, S. Imanparast, M.A. Faramarzi, M. Mahdavi, B. Larijani, New 6-amino-pyrido [2,3-*d*]pyrimidine-2,4-diones as novel agents to treat type 2 diabetes: a simple and efficient synthesis, *α*-glucosidase inhibition, molecular modeling and kinetic study, Eur. J. Med. Chem. 155 (2018) 353–363.

[27] Z. Heydari, M. Mohammadi-Khanaposhtani, S. Imanparast, M.A. Faramarzi, M. Mahdavi, P.R. Ranjbar, B. Larijani, Pyrano[3,2-*c*]quinoline derivatives as new class of α-glucosidase inhibitors to treat type 2 diabetes: synthesis, in vitro biological evaluation and kinetic study, Med. Chem. (2018), https://doi.org/10.2174/1573406414666180528110104.

[28] M. Taha, N.H. Ismail, S. Imran, A. Wadood, F. Rahim, S.M. Saad, K.M. Khan, A. Nasir, Synthesis, molecular docking and α-glucosidase inhibition of 5-aryl-2-(6′-nitrobenzofuran-2′-yl)-1,3,4-oxadiazoles, Bioorg. Chem. 66 (2016) 117–123.

[29] F. Rahim, F. Malik, H. Ullah, A. Wadood, F. Khan, M.T. Javid, M. Taha, W. Rehman, A.U. Rehman, K.M. Khan, Isatin based Schiff bases as inhibitors of α-glucosidase: synthesis, characterization, *in vitro* evaluation and molecular docking studies, Bioorg. Chem. 60 (2015) 42–48.